REMARKS

The Application has been reviewed in light of the Office Action mailed December 3, 2003. At the time of the Office Action, Claims 1-18 were pending in this Application. Claims 1-6 and Claim 18 have been withdrawn by Applicants due to an election/restriction requirement. Claims 7-17 are rejected. Applicants have amended Claim 7. This amendment does not present new matter. Applicants therefore respectfully request reconsideration and favorable action in this case.

Claim Objections

Claims 7-17 were objected to by the Examiner for containing zero amounts of ingredients other than pyruvate in the cardioplegia solution. Applicants appreciate the Examiner's attention to the claims. Applicants agree that at least some KCl is normally used in a cardioplegia solution to arrest the heart. Therefore Applicants have amended Claim 7 to recite at least 10 mM KCl in the cardioplegia solution. Applicants believe all other components listed in Claim 7, expect pyruvate, may be substitued with another compound or may be omitted from cardioplegia entirely. Whether to omit one or more components or to substitute another composition will be apparent to one skilled in the art.

Rejections under 35 U.S.C. §103

Claims 7-17 were rejected by the Examiner under 36 U.S.C. §103(a) as unpatentable over WO 93/02653 (the "WO 93 reference") taken with Rao et al. (the "Rao reference"), US 4,988,515 (the "'515" reference) and Tejero-Taldo et al. (the "Tejero reference"). The claims were rejected for reason previously presented and for additional reasons presented in the most recent Office Action.

The Examiner first argues that the WO 93 reference teaches a process for performing cardiopulmonary bypass surgery comprising heart arrest during cardiac operations by administering to the heart a cardioplegia solution having crystalloid solutions with concentrations within the ranges claimed in the present application. In response to this argument as previously presented by the Examiner, Applicants have argued that the WO 93 reference fails to teach pyruvate as a cardioplegia solution

ingredient. The Examiner, in the most recent Office Action, has indicated that Applicants' arguments were unconvincing.

Applicants therefore present additional arguments relating to the WO 93 reference. After further review of the WO 93 reference, Applicants believe it is apparent when examining the document taken as a whole that the ingredients listed in Table 1 of the document are contemplated solely for use as a crystalloid vehicle useful for production of the fluorocarbon emulsions of the reference. They are not contemplated as a cardioplegia for use absent fluorocarbons or other fluorochemicals. Thus the Examiner's assertion that the WO reference includes administering a cardioplegia solution *or* a cardioplegia emulsion/solution appears to overlook this significant distinction. While the WO 93 reference may well contemplate administration of a cardioplegia emulsion/solution containing a fluorocarbon or other fluorochemical, it does not in any way contemplate or teach or suggest the administration of a cardioplegia solution including the crystalloid solution of Table 1 alone. In fact, the WO 93 reference's focus on fluorochemicals if anything appears to indicate that the inventors of that reference did not even contemplate the use of the crystalloid solution in Table 1 of that reference as a cardioplegia solution amenable to independent administration. The focus on fluorochemicals in the claims of that reference provided further evidence of this focus. There is nothing in the WO 93 reference to suggest that the crystalloid solution in Table 1 was contemplated as anything other than a vehicle for a fluorochemical.

Applicants' cardioplegia of Claim 7 is not in any way indicated to be used as a vehicle for a fluorochemical, but rather functions as a cardioplegia in its own right. Therefore, Applicants assert that the WO 93 reference fails to teach or suggest at least one limitation of Claim 7. The other references cited by the Examiner also fail to teach or suggest a cardioplegia as claimed. Therefore, Applicants assert that Claim 7, as well as Claims 8-17, which are dependent thereon, are free from any prior art and are allowable.

The Examiner has also cited the Tejero reference as allegedly describing the beneficial effects of pyruvate-containing compositions in cardiac operations. Applicants have argued previously that Tejero teaches only an animal model that is not predictive of the results presented in the current Application. The Examiner

appears to indicate in the most recent Office Action that the WO 93 reference and the Rao reference teach human surgeries. While this may be true, WO 93 and the Rao reference present significantly different cardioplegia solutions and different methods than those disclosed in the present application and claimed in Claim 7. Just as an animal model is not dispositive of whether a cardioplegia is functional in humans, human tests with one substantially different type of cardioplegia solution are not necessarily indicative of whether a another cardioplegia solution will function in humans. This disparity, in fact, is the primary impetus for the development of different cardioplegia solutions. The unfortunate fact is that one cannot really determine how beneficial a cardioplegia solution differing from previous solutions by a major component, such as the energy source or presence of a fluorochemical, will be until human tests are done. After such tests, it is reasonable to assume that a given range of the major component will be functional, but it is not reasonable to assume that a radically changed cardioplegia solution will work simply because other cardioplegias have.

Additionally, Applicants respectfully point out that the Tejero reference is deficient not only because it involved an animal model, but also because it involves excised hearts perfused with saline. There are a large variety of differences between that situation and the examples presented in the present application, which provide data for intact hearts that remain in a patient and in contact with blood. Moreover, in the Tejero reference the neural connections between the heart and brain were severed, which disrupted control of cardiac function by the brain, whereas these neural connections were intact in the examples presented in the present application.

Additionally, the Tejero reference discloses experiments in which a heart was perfused with saline *after* an ischemic period. Applicants clearly indicate in Claim 7 that the cardioplegia is supplied to the heart *before* any ischemic period resulting from surgery. Although it may appear at first glance that effects observed by administration after ischemia may be generalized to predict effects that would result from administration during ischemia, this is actually not the case. It is well known that ischemic tissue is damaged and, as a result, experiences significant changes in its biochemical pathways. Additionally, release of cytokines by ischemic tissues and the body's subsequent response significantly alters the extracellular environment in

ischemic tissue. Many of these changes occur within 15 minutes of an ischemic event, but the Tejero reference presents experiments performed at least 15 minutes after the conclusion of ischemia. Because it is so well known in the cardiac field that ischemia rapidly induces significant changes in the ischemic tissue and even the nearby surrounding non-ischemic tissue, one skilled in the art would not find results of experiments with a composition administered several minutes after an ischemic event ends predictive of the effects of such a composition in preventing ischemic injury.

Accordingly, Applicants assert that there is no basis in the references cited to predict that the cardioplegia of the present invention would be effective in preventing ischemic damage to cardiac tissue during bypass surgery. Applicants therefore request allowance of Claims 7-17.

CONCLUSION

For the foregoing reasons, Applicants request that Claims 7-17 be allowed. Early and favorable acceptance of this application is respectfully requested.

Applicants believe no fee is due with this timely response. An RCE with appropriate fees is filed herewith. The Commissioner is hereby authorized to charge any fees or credit any overpayment to the Deposit Account No. 02-0384 of Baker Botts L.L.P.

Respectfully submitted,

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